Clostridium difficile Infection in the Department of Defense (DOD): 2007-2013

NMCPHC-EDC- TR-271-2015

By Charlotte Neumann and Uzo Chukwuma
EpiData Center Department
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14. ABSTRACT Reports of increased incidence and severity have renewed interest in the epidemiology of Clostridium difficile infection (CDI). This retrospective report summarizes trends for CDI for Department of Defense (DOD) and Department of the Navy (DON) beneficiaries from 2007-2013. CDI trends among both populations were similar and CDI incidence rates increased approximately 9.5% among all beneficiaries. Most notably, the increase occurred among beneficiaries with community-acquired (CA) CDI. For most DOD and DON beneficiaries, trends indicate that the vast majority of CDI were both acquired and identified in the community setting. The traditional risk factors (antibiotic use, ages 65 years and older and hospitalization) continue to be important to consider in the diagnostic evaluation of CDI. However, among all beneficiaries, the majority of CDI episodes were acquired in the community in ages ranging from 45 years and older. In addition, although most cases had an antibiotic prescribed in the 90 days before symptom onset, approximately 30% of beneficiaries did not have a history of antibiotic use. Therefore, providers should suspect CDI in any patient with acute inflammatory diarrhea including patients with no antibiotic use or healthcare facility exposures.			
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Abstract

Reports of increased incidence and severity have renewed interest in the epidemiology of Clostridium difficile infection (CDI). This retrospective report summarizes trends for CDI for Department of Defense (DOD) and Department of the Navy (DON) beneficiaries from 2007-2013. CDI trends among both populations were similar and CDI incidence rates increased approximately 9.5% among all beneficiaries. Most notably, the increase occurred among beneficiaries with community-acquired (CA) CDI. For most DOD and DON beneficiaries, trends indicate that the vast majority of CDI were both acquired and identified in the community setting. The traditional risk factors (antibiotic use, ages 65 years and older and hospitalization) continue to be important to consider in the diagnostic evaluation of CDI. However, among all beneficiaries, the majority of CDI episodes were acquired in the community in ages ranging from 45 years and older. In addition, although most cases had an antibiotic prescribed in the 90 days before symptom onset, approximately 30% of beneficiaries did not have a history of antibiotic use. Therefore, providers should suspect CDI in any patient with acute inflammatory diarrhea including patients with no antibiotic use or healthcare facility exposures.

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Executive Summary

The EpiData Center Department (EDC) at the Navy and Marine Corps Public Health Center (NMCPHC) conducts routine surveillance of clinically significant bacterial pathogens and antibiotic resistance patterns within the Department of Defense (DOD). This report provides a summary of *Clostridium difficile* infection (CDI) incidence for calendar years (CY) 2007-2013 and describes the demographics, clinical characteristics, and prescription practices observed among all DOD and Department of the Navy (DON) beneficiaries.

The Military Health System's (MHS) healthcare-related databases provide a unique opportunity to estimate the burden of CDI in both the inpatient and outpatient clinical settings. CDI cases were identified from positive *C. difficile* (CD) test results in Health Level 7 (HL7) formatted microbiology and chemistry databases. To estimate CDI acquisition, the collection date for a positive CD test was linked to the Standard Inpatient Data Record (SIDR) database. HL7 formatted pharmacy data were used to identify previous antibiotic use and CDI treatment.

CDI trends among DOD and DON beneficiaries were similar and incidence rates among both population increased approximately 9.5% from 2007-2013. Most notably, the increase occurred only among beneficiaries with community-acquired (CA) CDI. For most beneficiaries, trends indicate that the vast majority of CDIs were both acquired and identified in the community setting suggesting that exposures in the community environment may have had the greatest influence on CDI development.

The traditional risk factors (antibiotic use, advanced age, and hospitalization) continue to be important in the diagnosis of CDI. However, among all beneficiaries, the majority of CDI episodes were attributed to community exposure and were among those aged 45 years and older. In addition, although most cases had an antibiotic prescribed in the 90 days before CDI identification, approximately 30% of beneficiaries did not have a history of antibiotic use. Therefore, providers should also suspect CDI in any patient with diarrhea that includes patients with no history of antibiotic use or healthcare facility exposures.

Background

CD is a spore-forming, gram-positive anaerobic bacillus with both toxigenic and non-toxigenic strains. Toxin-negative strains are generally considered non-pathogenic, whereas toxigenic strains produce the major virulence determinants, toxin A and toxin B. Changes in the balance of normal colon flora that allow for massive colonization of toxigenic strains cause CDI, which manifests as diarrhea and pseudomembranous colitis.[1] Broad-spectrum antibiotic use is the most common cause of CD overgrowth in the colon and subsequent development of diarrhea.

Historically, CDI has been known as a hospital-acquired, antibiotic-associated diarrheal infection presenting in the immunocompromised and the elderly with comorbid conditions. Incidence has been relatively stable since 1978 when C. *difficile* was first identified as a causative agent in the majority of antibiotic-associated diarrhea cases.[2] However, in 2000, reports of increased incidence and severity renewed interest in the epidemiology of CDI.[3-4]Among patients admitted to United States (US) hospitals, the CDI incidence rate nearly doubled from 2001 to 2010 from 4.5 to 8.2 per 1,000 hospital discharges, respectively.[5] However, the investigators noted that incidence peaked in 2008 and declined slightly until 2010, suggesting that incidence among hospitalized patients was beginning to level off. More recently, CDI has become recognized in the community among patient populations previously described as low risk, including patients without prior exposure to antibiotics, peripartum women, patients with inflammatory bowel disease (IBD), and younger age groups (mean age, 26 years).[6-8] As community-acquired CDI surveillance has evolved, approximately 20-40% of CDI is reported to be community-acquired with an estimated incidence of 20-30 infections per 100,000 population.[9,10,37] The increase in incidence in both community and hospital acquired CDI over the last 20 years has been attributed to a combination of three main factors: the emergence of a previously rare and more virulent strain, NAP1/BI/027; inappropriate use of antibiotics; and an increase in the elderly population at risk.[11-14]

The most common risk factors for CDI have been antibiotic use, advanced age (i.e., 65 years of age or older), comorbidity, use of gastric acid suppressants, and prolonged hospitalization. Although antibiotic use is the primary CDI risk factor, several studies have reported CDI among antibiotic-naïve patients.[15,16] This finding has led to the investigation of other medications that have mechanisms of action able to influence CDI development. In February 2012, the Food and Drug Administration (FDA) informed the public that proton pump inhibitors (PPIs) may be associated with an increased risk of *C. difficile*–associated diarrhea.[17] Proton pump inhibitors decrease gastric acidity (pH), which provides pathogens the opportunity to colonize the normally sterile upper gastrointestinal (GI) tract, increasing the risk of enteric infections such as CDI. The FDA is reviewing the risk of CDI in users of histamine-2 (H2) receptor blockers. H2 receptor blockers may increase CDI risk due to suppression of gastric acid in the GI tract. However, the role of gastric acid suppressant use as an independent risk factor for CDI is controversial because of the association with certain comorbidities and concomitant use with antibiotics.[18,19]

Chronic disease is a risk factor for CDI patients not only due to the underlying disease, but also because of greater health care utilization and use of antibiotics to treat infectious complications

related to the chronic condition.[20] Specific chronic illnesses associated with CDI include chronic obstructive pulmonary disease (COPD), cancer, renal disease, and diabetes.[20,21] Khanna et al. found that CDI patients with high cumulative comorbidity predicted severe CDI and a greater need for hospitalization.[22] Therefore, comorbidity may predict which patients with CDI may be especially vulnerable to worse outcomes.

Diagnosis of CDI is based on recognizing clinical symptoms of diarrhea (greater than three non-formed stools in a 24 hour period) and confirming the diagnosis with laboratory testing for toxigenic strains of CD.[23] EIA testing of CD toxins A and B has been the most widely used test due to its rapid turnaround time and low cost. However, EIA has a sensitivity and specificity of approximately 75% and is no longer recommended as a standalone test.[24] In September 2010, the American Society for Microbiology (ASM) recommended the use of a NAAT to detect *C. difficile* toxin genes as a standalone diagnostic test, or the use of a two or three step testing algorithm with an initial screening glutamate dehydrogenase (GDH) assay and confirmation with either a toxin A/B EIA, cytotoxin neutralization, or a NAAT.[24] These testing methods have greater sensitivity than the EIA and, therefore, are expected to improve the ability to detect and manage CDI.

Antibiotic treatment is generally required for initial CDI episodes. The selection of antibiotic is dependent on the severity of disease, whether the episode is new or recurrent, and the patient's potential risk for recurrence.[25-26] Metronidazole and oral vancomycin have been the first-line antibiotics for an initial CDI treatment episode for over 25 years. However, neither metronidazole nor vancomycin is effective in preventing recurrent infection, which occurs in 10%-60% of patients.[27] In 2011, the FDA approved fidaxomicin as an alternative treatment for an initial recurrence or as an initial therapy for patients at high risk for recurrence. The new antibiotic was found to reduce recurrence by 45% as compared to vancomycin.[28] Fecal microbiota transplantation (FMT) with donor feces has become an effective treatment for recurrent CDI.[29] This treatment is based on the concept that the protective microbiome of natural colonic flora can be replaced to its former balanced state. FMT is not currently part of routine management.

Clearly, CDI has emerged as a major public health concern. The changing epidemiology, together with a highly virulent epidemic strain, has created a growing challenge for diagnosis, treatment, and infection control. Standardized surveillance methods can ensure timely tracking of CDI incidence and early identification of at-risk groups within the MHS beneficiary population.

Methods

This annual report is a retrospective surveillance summary for the period 01 January 2007 – 31 December 2013, assessing the burden and trends of CDI throughout the DON and DOD. The DON and DOD cohorts were selected from beneficiaries who received care at a fixed military treatment facility (MTF) during the surveillance period. The CDI cases were identified from positive CD test results in HL7 formatted microbiology and chemistry records. HL7 is a standard messaging format for the transmission of health-related data. Within the MHS, HL7 is used for the transmission of microbiology, pharmacy, anatomic pathology, chemistry, and radiology data that originates from a fixed MTF's Composite Health Care System (CHCS).

Figure 1 shows the lab-based surveillance algorithm based on published surveillance definitions used to categorize CD positive test results.[30] An incident CDI episode was defined as a positive CD test result with no positive CD test result in the previous eight weeks. An episode was considered recurrent if there was a positive CD test result after the most recent CD positive test result. CD positive test results dated within two weeks of the prior positive CD test were considered duplicate cases and were excluded from analysis.

Incident CDI episodes were further classified into four categories to approximate CDI acquisition using the positive CD test collection date, a proxy for symptom onset, and the presence of an inpatient encounter in SIDR which captured potential hospital exposure. [26] In brief, each acquisition category provides information regarding the specific environment (community or hospital) that may have influenced CDI development. SIDR is the electronic database used to record inpatient healthcare services provided to DOD beneficiaries at fixed MTFs. These records contain International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, patient demographics, and codes for servicing MTFs and clinics. Continuous admissions, readmissions, or transfers of one day or less were combined and counted as a single admission to more accurately reflect the beneficiary's length of exposure to the hospital environment.

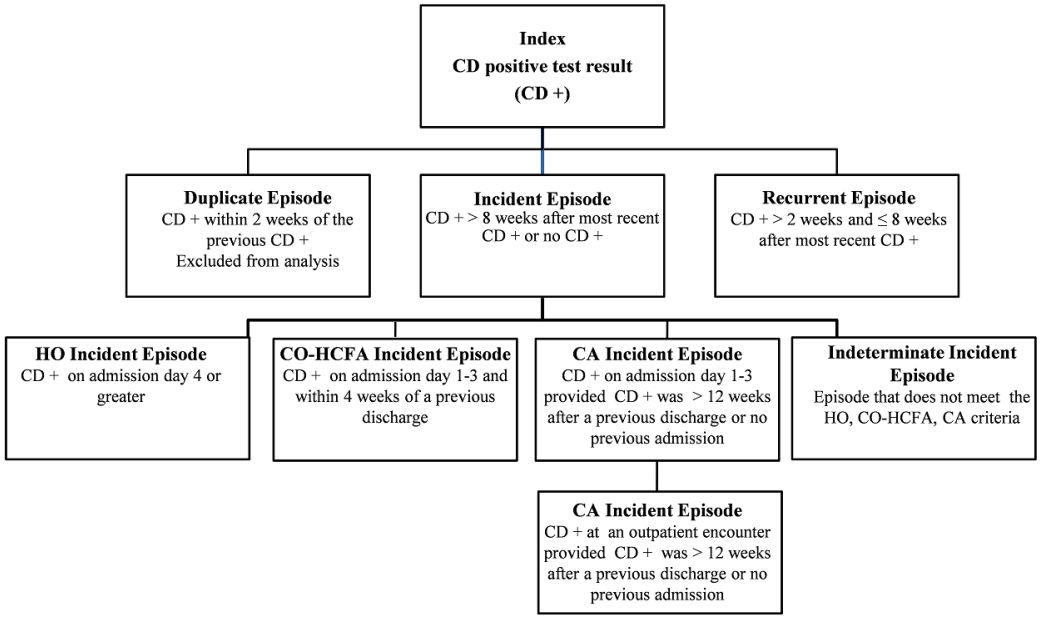
- Hospital-onset (HO): HO CDI incident episodes were acquired in the hospital based on the CD collection date. CD positive test results with collection dates on day four or greater of the inpatient admission establish that the patient developed CDI in the hospital.

- Community-onset, healthcare facility associated (CO-HCFA): CO-HCFA CDI episodes were related to CD symptom onset in the community based on the positive CD test collection date, but the history of hospital admission may have influenced the development of CDI. CD positive test results with a collection date on days one, two, or three of the inpatient admission were used to establish that the CDI symptom onset was in the community and a previous hospital discharge within four weeks of the current CD collection date established that the exposures in the hospital environment influenced CDI development.

- Community-acquired (CA): CA CDI incident episodes acquired in the community based on the timing of the CD positive test result. Consequently, hospital admission was not considered a factor in CDI development. The CA incident episode category includes positive CD test positive results that were collected during an ambulatory encounter with no previous hospital discharge or no hospital discharge within 12 weeks of the current CD collection date. The category may also include positive CD test results with collection dates within three days of the inpatient admission and no previous hospital discharge within 12 weeks of the most recent collection date.

- Indeterminate: The indeterminate incident episode category includes positive CD test results that did not meet the hospital-onset, community-onset healthcare facility associated, or community-acquired case definitions.

Figure 1. *C. difficile* Lab-Based Surveillance Algorithm



Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Incident CDI episodes were additionally characterized by the encounter type (inpatient or outpatient) to determine the clinical location in which the episode was identified. Identification relates only to the clinical location where the patient had a CD positive test result. Therefore, this measure is not necessarily reflective of CDI acquisition. A Medical Expense and Performance Reporting System (MEPRS) code of "A" in the HL7 microbiology and chemistry record indicated that the episode was identified in an inpatient location; all other MEPRS codes indicated that the episode was identified in an outpatient location.

Descriptive Analysis

Descriptive analysis was performed to examine trends for both incident CDI episodes and beneficiaries with CDI. Because a beneficiary can have more than one incident episode, CDI analysis includes all characteristic values for incident episodes that occurred during the six year surveillance period. In contrast, beneficiary demographic characteristics reflect the values obtained from the index incident episode.

Demographic data were collected from the HL7 microbiology and chemistry record for each beneficiary. The TRICARE region was defined by the region of the servicing MTF identified by the requesting facility Defense Medical Information System (DMIS) identification number (ID) indicated in the HL7 microbiology record. Age was defined as the beneficiary's age at the date of specimen collection. Sponsor service and beneficiary status were identified by the patient category (PATCAT) code, where the first letter indicates the service of the sponsor (Air Force, Army, Marine Corps, or Navy) and the two subsequent numbers indicate beneficiary status (active duty service member, retiree, family member, or other). For this analysis, the beneficiary category "Active Duty" included both active duty service members and recruits. The beneficiary category "Family Members" included family members of active duty service members and retirees only; all other family members and beneficiaries (including National Guard members, reservists, and civilians) were given the beneficiary category designation of "Other."

The Charlson Comorbidity Index (CCI) was used to determine the number of coexisting medical diagnoses among CDI beneficiaries using the method adapted by Deyo and Quan for use with administrative databases containing ICD-9-CM codes.[31-33] Seventeen different diagnosis categories with multiple ICD-9-CM codes for each category are used in the CCI including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complications, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy including leukemia and lymphoma, moderate or severe liver disease, metastatic solid tumors, and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). Each category was assigned a weight based on the severity of the disease. The weighted sum of the conditions was created and the sum became the CCI score, which can range from 0 - 27. A CCI score of zero means the CDI beneficiary had no comorbidities identified during the study period. Higher scores describe which CDI beneficiaries may have poorer health outcomes.[22] SIDR and the ambulatory database were used to create the CCI for beneficiaries. The ambulatory database contains records of outpatient healthcare services provided to DOD beneficiaries at fixed MTFs. These records contain ICD-9-CM diagnoses and procedure codes, patient demographics, and codes for servicing MTFs and clinics.

Prescriptions transactions for metronidazole, vancomycin, or fidaxomicin seven days before or after each incident CDI episode collection date were used to examine *C. difficile* antibiotic treatment. Prescriptions ordered in the seven-day period before the CD positive test result were applied to account for presumptive treatment. Previous antibiotic use was determined from

pharmacy prescriptions transacted within the previous 90 days for each incident episode collection date. Vancomycin, metronidazole, and fidaxomicin were excluded from the previous antibiotic use analysis because these antibiotics are used for CDI treatment. Any antibiotic prescribed from the selected antibiotic classes in Table 1 were included for previous antibiotic use analysis. PPI (dexlansprazole, esomeprazole magnesium, lansoprazole, omeprazole, rabeprazole) and H2 antagonist (cimetidine, famotidine, nizatidine, ranitidine) use were also evaluated in the previous 90 days of the incident CDI episode collection date. Previous antibiotic use, gastric suppressant use, and CDI treatment were determined from HL7 pharmacy records available from 2010-2013. The HL7 pharmacy data source contains three pharmacy data types:: outpatient (OP), unit-dose (UD), and intravenous (IV) that are consistently complete beginning in 2010.

Table 1. Selected Antibiotic Classes

Aminoglycosides
Carbapenems
Cephalosporins (generations 1-4)
Clindamycin
Fluoroquinolones
Metronidazole
Penicillins/penicillin beta-lactam inhibitors
Sulfonamides and/or trimethoprim
Tetracycline
Other[a]

[a]Colistin, capreomycin, ethionamide, fosfomycin, isoniazid monobactam, nitrofurantoin, novobiocin, polymixin B, pyrazinamide, rifampin, spectinomycin, and para-aminosalicylic acid.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Population-based incidence rates are presented to provide a measure of the annual frequency of new CD episodes in the MHS population. In calculating incidence rates, population estimates for 2007-2013 were derived from the MHS Mart (M2) database using the mid-year eligible beneficiary population estimates for both the DOD and DON for each year. Annual incidence rates were expressed as the number of incident episodes per 100,000 eligible beneficiaries per year. Calculations for population-based annual incidence rates are presented in Table 2.

Table 2. Calculation for Annual Population-Based CDI Incidence Rates per 100,000 Eligible Beneficiaries

CDI Incidence Rate

$$\frac{\text{Number of CDI incident episodes}}{\text{Mid-year eligible beneficiary population per year}} \times 100{,}000$$

CDI HO Incidence Rate - Infection Acquisiton Measure

$$\frac{\text{Number of HO CDI incident episodes}}{\text{Mid-year eligible beneficiary population per year}} \times 100{,}000$$

CDI CO-HCFA Incidence Rate - Infection Acquisiton Measure

$$\frac{\text{Number of CO-HCFA CDI incident episodes}}{\text{Mid-year eligible beneficiary population per year}} \times 100{,}000$$

CDI CA Incidence Rate - Infection Acquisiton Measure

$$\frac{\text{Number of CA CDI incident episodes}}{\text{Mid-year eligible beneficiary population per year}} \times 100{,}000$$

CDI Indeteminate Incidence Rate - Infection Acquisiton Measure

$$\frac{\text{Number of Indeterminate CDI incident episodes}}{\text{Mid-year eligible beneficiary population per year}} \times 100{,}000$$

CDI Outpatient Encounter Incidence Rate - Clinicial Setting Measure

$$\frac{\text{Number of outpatient encounter CDI incident episodes}}{\text{Mid-year eligible beneficiary population per year}} \times 100{,}000$$

CDI Inpatient Encounter Incidence Rate - Clinicial Setting Measure

$$\frac{\text{Number of inpatient encounter CDI incident episodes}}{\text{Mid-year eligible beneficiary population per year}} \times 100{,}000$$

Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Inpatient incidence rates are presented to provide a measure of the annual frequency of new CD episodes that occur during MTF hospitalizations. Patient-days are used to estimate the number of days that a beneficiary is at risk for CDI for each year. Annual inpatient incidence rates were expressed as the number of incident episodes per 10,000 patient days per year. Calculations for inpatient incidence rates are presented in Table 3.

Table 3. Calculation for Annual CDI Inpatient Incidence Rates per 10,000 Patient-Days

CDI Inpatient Incidence Rate

$$\frac{\text{Number of CDI inpatient incident episodes}}{\text{Number of patient-days per year}} \times 10{,}000$$

CDI HO Incidence Rate - Infection Acquisiton Measure

$$\frac{\text{Number of HO CDI inpatient incident episodes}}{\text{Number of patient-days per year}} \times 10{,}000$$

CDI CO-HCFA Incidence Rate - Infection Acquisiton Measure

$$\frac{\text{Number of CO-HCFA CDI inpatient incident episodes}}{\text{Number of patient-days per year}} \times 10{,}000$$

CDI Combined HO and CO-HCFA - Combined Hospital Acquired Infection Measure

$$\frac{\text{Number of Indeterminate inpatient CDI incident episodes}}{\text{Number of patient-days per year}} \times 10{,}000$$

CDI Inpatient CA Incidence Rate - Infection Acquisiton Measure

$$\frac{\text{Number of CA CDI inpatient incident episodes}}{\text{Number of patient-days per year}} \times 10{,}000$$

CDI Indeteminate Incidence Rate - Infection Acquisiton Measure

$$\frac{\text{Number of Indeterminate inpatient CDI incident episodes}}{\text{Number of patient-days per year}} \times 10{,}000$$

Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Annual admission prevalence rates are presented to provide a measure of the annual frequency of CDI importation into military hospitals. Annual admission prevalence rates were expressed as the number of incident episodes per 10,000 admissions per year. Calculations for admission prevalence rates are presented in Table 4.

Table 4. Calculation for Annual CDI Admission Prevalence Rates per 10,000 Admissions

CDI Admission Prevalence Rate - Combined Hospital Importation Measure

$$\frac{\text{Number of CDI inpatient CA and CO-HCFA non-duplicate episodes}}{\text{Number of admissions per year}} \times 10{,}000$$

CDI Admission Prevalence Rate - Hospital Importation Measure

$$\frac{\text{Number of inpatient CA CDI non-duplicate episodes}}{\text{Number of admissions per year}} \times 10{,}000$$

CDI Admission Prevalence Rate - Hospital Importation Measure

$$\frac{\text{Number of inpatient CO-HCFA CDI non-duplicate episodes}}{\text{Number of admissions per year}} \times 10{,}000$$

Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Outpatient prevalence rates were evaluated to provide a measure of the annual burden of CDI presenting to ambulatory clinics at fixed MTFs. The numerator for the outpatient prevalence rate included incident and recurrent CDI episodes. The denominator included the number of outpatient encounters for all MTF ambulatory clinics. The outpatient prevalence rate was expressed as the number of incident and recurrent episodes per 100,000 outpatient encounters per year. Outpatient encounter records were derived from the ambulatory database.

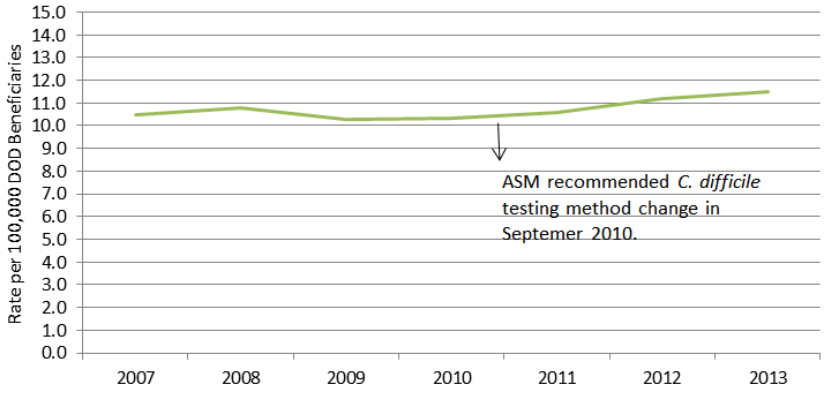
Results

DOD Results

CDI Incidence Rates

From 2007-2013, a total of 7,173 CDI incident episodes occurred among 6,779 DOD beneficiaries. Over the same period, annual incidence rates increased 9.5% from 10.5 to 11.5 per 100,000 person-years (Figure 2). The incidence rate increase was not uniform as rates decreased 1.9% from 2007-2009 and increased 11.6% from 2010-2013, the period following ASM recommendations to change to more sensitive and specific CD testing methods.

Figure 2. CDI Incidence Rates among DOD Beneficiaries, 2007-2013[a]

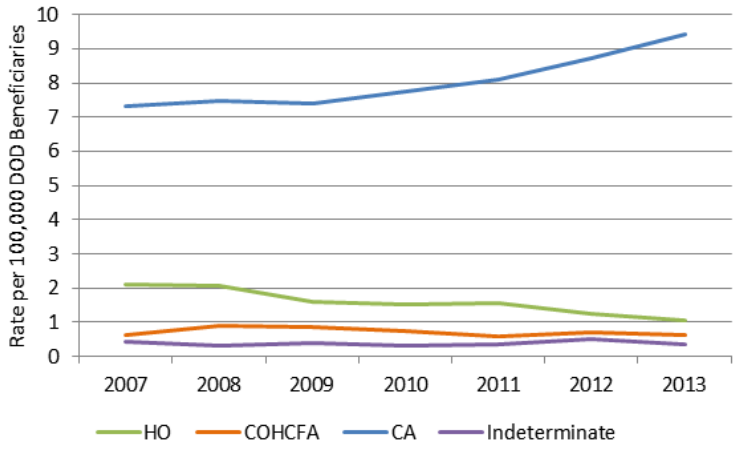


[a]*Clostridium difficile* Infection (CDI) incident episodes (N = 7173).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and MHS Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Incidence Rates by Acquisition Category

The majority of the 7,173 CDI incident episodes were acquired in the community setting (74.9%) compared to HO (14.8%), CO-HCFA (6.7%), and indeterminate (3.7%) acquistion. The CA incident episode dominance is also observed in the relative difference between CA CDI incidence rates that were 3.5 to 9.0 times higher than HO CDI incidence rates. The trend toward greater CA acquistion is repeated in the rate change from 2007 to 2013 where CA CDI incidence rates increased 28.8% from 7.3 to 9.4 per 100,000 person-years (Figure 3). In contrast, HO CDI decreased 47.6% from 2.1 to 1.1 per 100,000 person-years. CO-HCFA and indeterminate CDI incidence rates were well below CA and HO incidence rates throughout the period. In addition, any CO-HCFA or indeterminate annual incidence rate flucutations were unremarkable compared to CA and HO incidence rates (Figure 3).

Figure 3. CDI Incidence Rates by Acquisition Category among DOD Beneficiaries, 2007-2013[a]

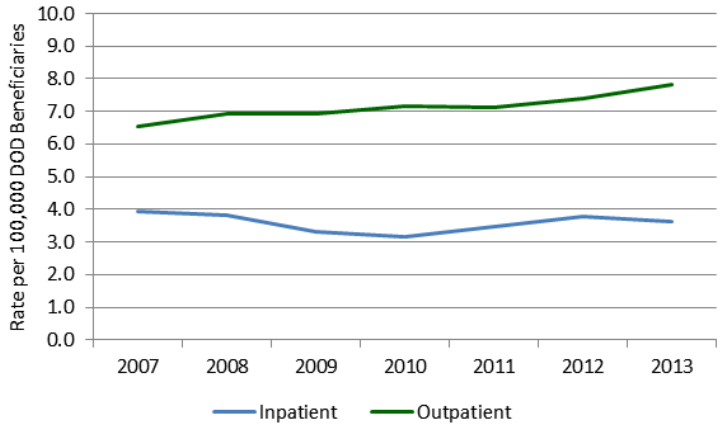


[a]*Clostridium difficile* Infection (CDI) incident episodes: (Hospital Onset (HO), n = 1061), (Community Onset (CO), n = 5373), (Community Onset Healthcare Facility Associated (CO-HCFA), n = 481), (indeterminate, n = 258).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and MHS Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Rates by Clinical Setting

From 2007-2013, most CDI incident episodes were identified in the outpatient setting compared to the inpatient setting (66.6% vs. 34.2%, respectively). Throughout the period, incidence rates in the outpatient setting were approximately two-fold higher than incidence rates in the inpatient setting (Figure 4). The trend toward greater CDI identification in the outpatient setting also appears in the relative difference in rates from 2007 to 2013, where CDI incidence rates in the outpatient setting increased 18.2% from 6.6 to 7.8 per 100,000 person-years, whereas CDI incidence rates in the inpatient setting decreased 7.7% from 3.9 to 3.6 per 100,000 person-years.

Figure 4. CDI Incidence Rates by Clinical Setting among DOD Beneficiaries, 2007-2013[a]



[a]*Clostridium difficile* Infection (CDI) incident episodes: (inpatient, n = 4777) and (outpatient, n = 2396).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and MHS Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Select Demographic Characteristics

The demographic distribution of CDI among DOD beneficiaries did not vary over time (data not shown). CDI was more likely to occur among family members (54.8%), individuals aged 45 years and older (49.8%), beneficiaries seen at MTFs in the West TRICARE region (34.5%), and females (52.1%) (Table 5). Metronidazole remained the first-line medication used for an initial CDI episode (data not shown).

Approximately 8.0% (n = 545) of beneficiaries experiencing an incident CDI episode also experienced a recurrent CDI episode. The mean number of days from the initial incident episode to the recurrent episode was 30 days). The demographic distribution of patients with recurrence was similar to patients who experienced an incident episode (data not shown).

Table 5. Distribution of Selected Demographic Characteristics among DOD Beneficiaries with CDI, 2007-2013

N = 6779[a]	Count	Percent
Gender		
Female	3571	52.7
Male	3208	47.3
Age Group		
0-17 years	1002	14.8
18-24 years	723	10.7
25-34 years	929	13.7
35-44 years	745	11.0
45-64 years	1642	24.2
> 65 years	1738	25.6
Sponsor Service		
Air Force	2020	26.4
Army	2667	34.8
Marine Corps	525	6.9
Navy	1567	20.5
Beneficiary Type		
Active duty	1359	20.0
Family Member	3717	54.8
Retired	1500	22.1
Other	203	3.0
TRICARE Region[b]		
Alaska	128	1.7
North	2164	28.2
OCONUS	246	3.2
South	1591	20.8
West	2646	34.5

[a]The demographics presented represent the values obtained from the index incident episode during 2007-2013.
[b]Four patient records had missing TRICARE region values.
Data Sources: NMCPHC HL7 formatted microbiology and chemistry databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Cumulative Comorbidity Burden among CDI Patients

Approximately 30.8% of DOD beneficiaries had a diagnosis of at least one of the comorbid medical conditions included in the CCI within a year of the incident CDI episode (Table 6). The mean number of comorbidities among CDI patients was 2.4 (1.4, standard deviation). A relatively small percentage (15.9%) of beneficiaries had a CCI score greater than 2; the burden of comorbidities and potential risk of poor health outcomes were higher compared to beneficiaries with CCI scores less than 2 (84.2%). The five most frequent medical conditions among beneficiaries with a comorbidity were chronic pulmonary disease, any cancer, diabetes, renal disease, and congestive heart failure.

Table 6. Selected Comorbid Medical Conditions among DON Beneficiaries with CDI, 2007-2013

	Count	Percent
Any Selected Comorbidty [a]	2058	30.4
Charlson Comorbidty Index Score [a]		
0	4864	71.8
1-2	838	12.4
3-4	490	7.2
5+	587	8.7
Select Comorbid Medical Conditions [b]		
Myocardial Infarction	305	14.8
Congestive heart failure	508	24.7
Peripheral vascular disease	283	13.8
Cardiovascular disease	212	10.3
Hemiplegia or paraplegia	57	2.8
Dementia	109	5.3
Chronic pulmonary disease	655	31.8
Rheumatological disease	108	5.2
Peptic ulcer disease	104	5.1
Diabetes without chronic complications	183	8.9
Diabetes with chronic complications	474	23.0
Renal disease	614	29.8
Any malignancy including leukemia and lymphoma	391	19.0
Metastatic solid tumor	178	8.6
Mild liver disease	153	7.4
Moderate or severe liver disease	71	3.4
AIDS/HIV	0	--

[a]Percentages are calculated from the number of patients who experienced an incident *Clostridium difficile* Infection (CDI) episode during 2007-2013 (N = 6779).
[b]The percentage is determined from the number of CDI patients who experienced a comorbidity (n = 2058).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, SIDR, and ambulatory databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Previous Antibiotic and Gastric Acid Inhibitor Use

Table 7 shows that nearly 68.5% of CDI incident episodes occurring between 2010-2013 had an antibiotic prescribed within the previous 90 days. In addition, the average number of antibiotic classes prescribed was approximately two per beneficiary. The top three antibiotic classes prescribed were fluoroquinolones, cephalosporins (generations 1-4), and penicillin beta-lactam inhibitors. Approximately 48% of CDI incident episodes had a gastric acid inhibitor prescribed before the incident event (PPIs (37.1%) and H2 receptor anatagonists (11.0%)).

Table 7. Selected Medications Prescribed in the 90 Days Before a CDI Incident Episode among DOD Beneficiaries, 2010-2013

	Count	Percent
Antibiotic Therapy [a]		
	2686	68.5
Antibiotic Classes [b]		
Fluoroquinolones	1294	48.2
Cephalosporins (generations 1-4)	1045	38.9
first generation	385	14.3
second generation	88	3.3
third generation	414	15.4
fourth generation	158	5.9
Penicillin beta-lactam inhibitors	691	25.7
Clindamycin	500	18.6
Penicillins	483	18.0
Sulfonamides and/or trimethoprim	347	12.9
Macrolides	320	11.9
Carbapenems	257	9.6
Other	254	9.5
Aminoglycosides	145	5.4
Tetracycline	112	4.2
Gastric Acid Inhibitors [a]		
Proton Pump Inhibitor	1455	37.1
H2 Receptor Blocker	430	11.0

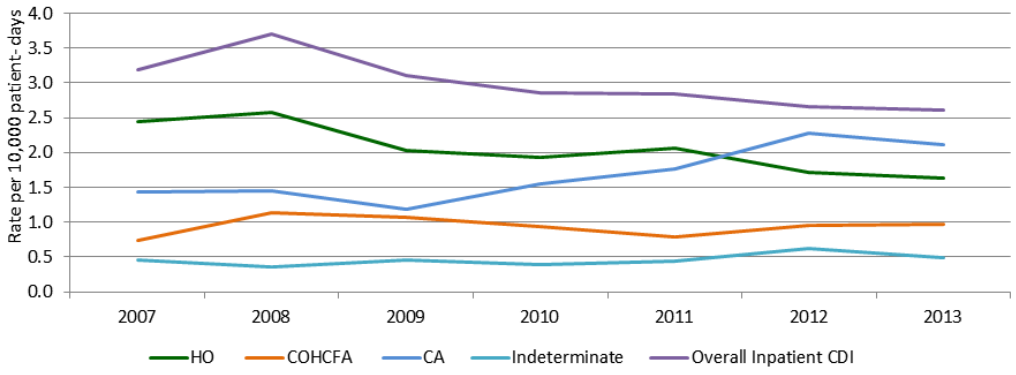
[a]The percentage is determined from the number of incident *Clostridium difficile* Infection (CDI) episodes during 2010-2013 (N = 3923).
[b]The percentage is determined from the number of incident CDI episodes with antibiotic prescribed in the previous 90 days (n = 2686).
Data Sources: NMCPHC HL7 formatted microbiology, chemistry, and pharmacy databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Inpatient Incidence Rates

Approximately 37.0% of the 7,173 incident CDI episodes from 2007-2013 were inpatient episodes. The overall inpatient CDI incidence rate peaked in 2008 and decreased 18.7% by 2013 (Figure 5). The decrease in the overall inpatient incidence rate during the seven year surveillance period was influenced by the change in the distribution of the two most frequent types of acquistion among inpatient CDI episodes, CA (32.1%) and HO (40.0%). Accordingly, among hospitalized beneficiaries, the frequency of CA acquistion increased from 28.1% in 2007 to 40.1% in 2013 and the frequency of HO acquisition decreased from 47.8% in 2007 to 31.0 % in 2013. Hence, CA incidence rates increased 50.0% while HO inpatient incidence rates decreased 33.3%. Additionally, HO incidence rates were 1-2 fold higher than CA incidence rates until 2012-2013, when CA rates surpassed HO rates.

Inpatient incidence rates attributed to hospital acquisition (combined HO and CO-HCFA) decreased 18.2%. HO inpatient incidence rates were 1.8 to 3.3 fold higher than CO-HCFA rates, suggesting that HO cases were the main driver of hospital acquistion rates (data not shown). However, the relative difference between HO and CO-HCFA rates is decreasing.

Figure 5. Inpatient Incidence Rates per 10,000 Patient-Days by Acquisition Category among DOD Beneficiaries, 2007-2013[a]

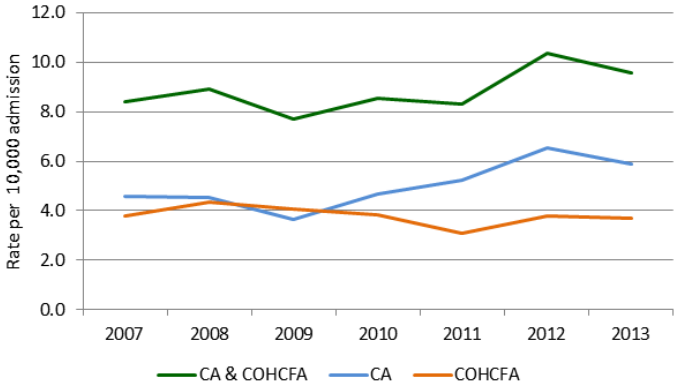


[a]*Clostridium difficile* Infection (CDI) inpatient incidence episodes (n = 1542).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and SIDR databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Admission Prevalence Rates

Overall admission prevalence (combined CA and CO-HCFA), a proxy for CDI importation into MTFs, showed a peak year-to-year increase of 25.3% in 2012 with a total surveillance period increase of 14.3% (Figure 6). Analysis of admission prevalence rates stratified by acquisition demonstrated that annual CO-HCFA incidence rates were slightly higher than CA rates in 2007 and 2009, after which CA rates were consistently higher for the remainder of the period.

Figure 6. CDI Admission Prevalence Rates among DOD Beneficiaries, 2007-2013[a]

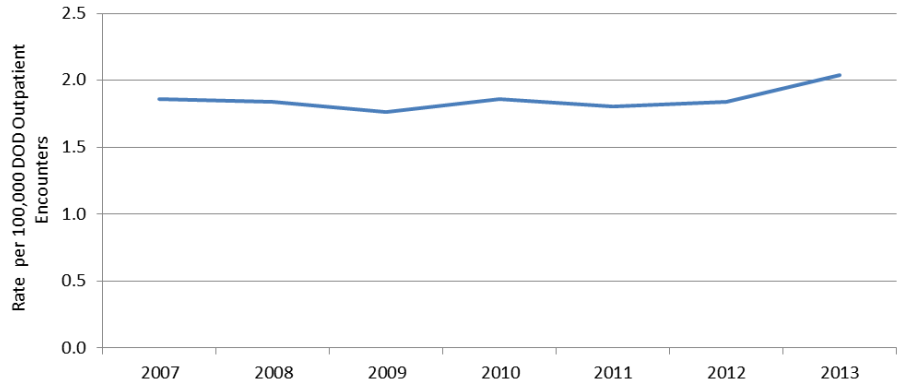


[a]*Clostridium difficile* Infection (CDI) admission prevalent episodes: (Community Associated (CA), n = 853) and (Community Onset Healthcare Facility Associated (CO-HCFA), n = 539).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and MHS Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Outpatient Prevalence Rates

Outpatient prevalence rates at ambulatory clinics increased 5.3% from 2007 – 2013 (Figure 7). However, year-to-year variation remained stable, with less than one percent change in either direction.

Figure 7. Outpatient Prevalence Rates per 100,000 Patient-Encounter among DOD Beneficiaries, 2007-2013[a]



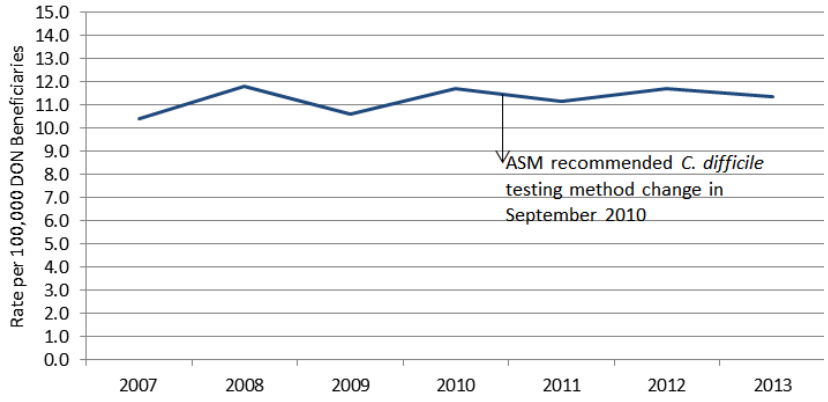
[a]*Clostridium difficile* Infection (CDI) outpatient prevalent episodes (n = 5857).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and ambulatory databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

DON Results

CDI Incidence Rates

From 2007-2013, a total of 2,238 CDI incident episodes occurred among 2,092 DON beneficiaries. Over the same period, annual incident rates increased 9.6% from 10.4 to 11.4 per 100,000 person-years (Figure 8). The incidence rate increase was not uniform as rates increased 1.9% from 2007-2009 and decreased 3.4% from 2010-2013, the period following ASM recommendations to change to more sensitive and specific CD testing methods. In addition, the 2010-2013 incidence rates showed less variation (range 11.1 – 11.7 per 100,000 person-years) compared to the 2007-2009 rates (range 10.4 – 11.8 per 100,000 person-years).

Figure 8. CDI Incidence Rates among DON Beneficiaries, 2007-2013[a]

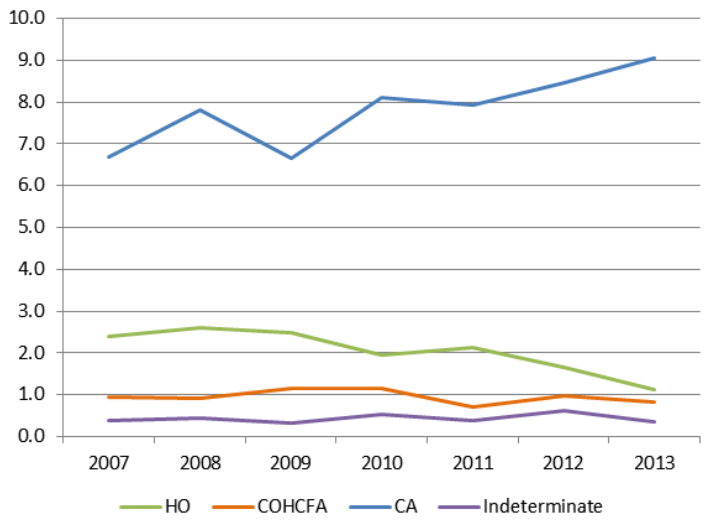


[a]*Clostridium difficile* Infection (CDI) incident episodes (N = 2238).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and MHS Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Incidence Rates by Acquisition Category

The majority of the 2,238 inpatient CDI incident episodes were acquired in the community (CA) (69.4%) compared to HO (18.3%), CO-HCFA (8.5%), and indeterminate (4.0%) acquistion. The CA incident episode dominance is also observed in the relative difference between CA CDI incidence rates that were 2.8 to 7.9 fold higher than HO CDI incidence rates (Figure 9). The trend toward greater CA acquistion is repeated in the rate change from 2007 to 2013 where CA CDI incidence rates increased 35.8% from 6.7 to 9.1 per 100,000 person-years. In contrast, HO CDI incidence rates decreased 54.2% from 2.4 to 1.1 per 100,000 person-years. CO-HCFA and indeterminate CDI incidence rates were well below CA and HO incidence rates throughout the period.

Figure 9. CDI Incidence Rates by Acquisition Type among DON Beneficiaries, 2007-2013[a]

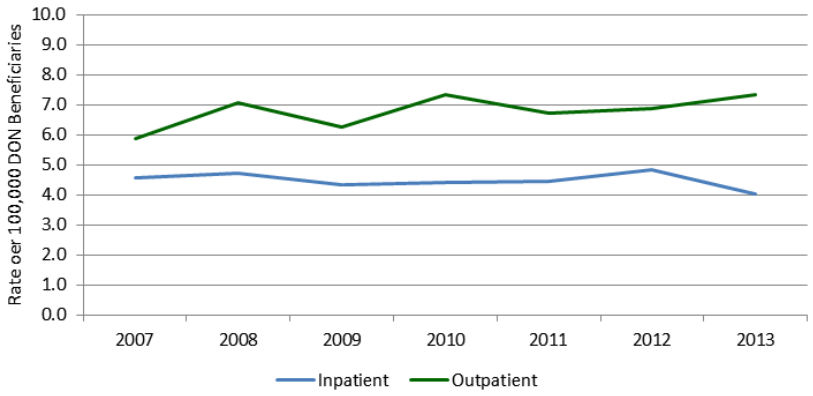


[a]*Clostridium difficile* Infection (CDI) incident episodes: (Hospital Onset (HO), n = 409), (Community Associated (CA), n = 1552), (Community Onset Healthcare Facility Associated (CO-HCFA), n = 190), (indeterminate, n =87).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and MHS Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Rates by Clinical Setting

From 2007-2013, most CDI incident episodes were identified in the outpatient setting compared to the inpatient setting (60.2% vs. 39.8%, respectively). Throughout the period, incidence rates in the outpatient setting were approximately 1.3 to 1.8 fold higher than incidence rates in the inpatient setting (Figure 10). The trend toward greater CDI identification in the outpatient setting is also observed in the relative difference in rates from 2007 to 2013, where CDI incidence rates in the outpatient setting increased 23.7% from 5.9 to 7.3 per 100,000 person-years, whereas CDI incidence rates in the inpatient setting decreased 13.0% from 4.6 to 4.0 per 100,000 person-years.

Figure 10. CDI Incidence Rates by Clinical Setting among DON Beneficiaries, 2007-2013[a]



[a]Outpatient *Clostridium difficile* Infection (CDI) episodes (n = 1348) and inpatient CDI episodes (n = 890).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and MHS Mart (M2) databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Select Demographic Characteristics

The demographic distribution of CDI among DON beneficiaries did not vary over time (data not shown). CDI was more likely to occur among family members (54.3%), individuals aged over 45 years (46.6%), the West TRICARE region (51.4%), and males (51.0%) (Table 8). Metronidazole remained the first-line medication used for an initial CDI episode (data not shown).

Approximately 8.7% (n = 183) of beneficiaries experiencing an incident episode also experienced a recurrent episode. The mean number of days from the initial episode to the recurrent episode was 29.8 days (range 15-56 days). The demographic distribution of patients with recurrence was similar to patients who experienced an incident episode (data not shown).

Table 8. Distribution of Selected Demographic Characteristics among DON Beneficiaries with CDI, 2007-2013[a]

N = 2092	Count	Percent
Gender		
Female	1025	49.0
Male	1067	51.0
Age Group		
0-17 years	335	16.0
18-24 years	276	13.2
25-34 years	295	14.1
35-44 years	211	10.1
45-64 years	467	22.3
>65 years	508	24.3
Sponsor Service		
Marine Corps	525	25.1
Navy	1567	74.9
Beneficiary Type		
Active duty	465	22.2
Family Member	1137	54.3
Retired	446	21.3
Other	44	2.1
TRICARE Region[b]		
Alaska	2	0.1
North	703	33.6
OCONUS	55	2.6
South	255	12.2
West	1076	51.4

[a]The demographics presented represent the values obtained from the index incident episode during 2007-2013.
Data Sources: NMCPHC HL7 formatted microbiology and chemistry databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Cumulative Comorbidity Burden

Approximately 31.5% of DON beneficiaries had a diagnosis of at least one of the comorbid medical conditions included in the CCI within a year of the CDI incident episode (Table 9). The mean number of comorbidities among CDI patients was 2.2 (standard deviation, 1.5). A relatively small percentage (17.9%) of beneficiaries had a CCI score greater than 2; meaning that the burden of comorbidities and potential risk of poor health outcomes were higher compared to beneficiaries with CCI scores less than 2 (82.0%). The five most frequent medical conditions were chronic pulmonary disease, any cancer, diabetes, renal disease, and congestive heart failure.

Table 9. Selected Comorbid Medical Conditions among DON Beneficiaries with CDI, 2007-2013

	Count	Percent
Any Selected Comorbidty [a]	658	31.5
Charlson Comorbidty Index Score [a]		
0	1434	68.5
1-2	283	13.5
3-4	178	8.5
5+	197	9.4
Select Comorbid Medical Conditions [b]		
Myocardial Infarction	79	12.0
Congestive heart failure	170	25.8
Peripheral vascular disease	70	10.6
Cardiovascular disease	68	10.3
Hemiplegia or paraplegia	26	4.0
Dementia	38	5.8
Chronic pulmonary disease	219	33.3
Rheumatological disease	38	5.8
Peptic ulcer disease	35	5.3
Diabetes without chronic complications	152	23.1
Diabetes with chronic complications	51	7.8
Renal disease	203	30.9
Any malignancy including leukemia and lymphoma	142	21.6
Metastatic solid tumor	70	10.6
Mild liver disease	63	9.6
Moderate or severe liver disease	34	5.2
AIDS/HIV	0	--

[a]The percentage is determined from the number of patients who experienced an incident episode during 2007-2013 (N = 2092).
[b]The percentage is determined from the number of *Clostridium difficile* Infection (CDI) patients who experienced a comorbidity (n = 658).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, SIDR, and ambulatory databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Previous Antibiotic and Gastric Acid Inhibitor Use

Table 10 shows that nearly 66.5% of CDI incident episodes had an antibiotic prescribed within the previous 90 days. In addition, the average number of antibiotic classes prescribed was approximately two per beneficiary. The top three antibiotic classes prescribed were fluoroquinolones, cephalosporins (generations 1-4), and penicillin beta-lactam inhibitors. Approximately 48.0% of CDI incident episodes had a gastric acid inhibitor prescribed before the incident event (PPIs (36.3%) and H2 receptor anatagonists (11.3%)).

Table 10. Selected Medication Use in the 90 Days before a CDI Incident Episode among DON Beneficiaries, 2010-2013

	Count	Percent
Antibiotic Therapy [a]		
	869	66.5
Antibiotic Classes [b]		
Fluoroquinolones	417	48.0
Cephalosporins (generations 1-4)	389	44.8
first generation	118	13.6
second generation	50	5.8
third generation	158	18.2
fourth generation	63	7.2
Penicillin beta-lactam inhibitors	229	26.4
Penicillins	161	18.5
Clindamycin	148	17.0
Sulfonamides and/or trimethoprim	114	13.1
Macrolides	101	11.6
Carbapenems	97	11.2
Other	80	9.2
Aminoglycosides	65	7.5
Tetracycline	29	3.3
Gastric Acid Inhibitors [a]		
Proton Pump Inhibitor	474	36.3
H2 Receptor Blocker	147	11.3

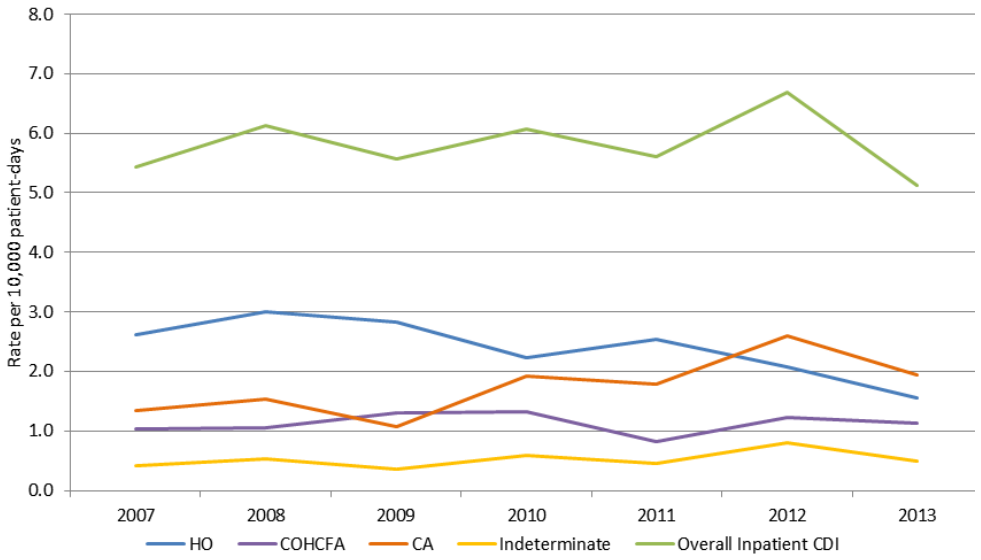
[a]The percentage is determined from the number of incident *Clostridium difficile* Infection (CDI) episodes during 2010-2013 (N = 1306).
[b]The percentage is determined from the number of CDI episodes with an antibiotic prescribed in the previous 90 days (n = 869).
Data Sources: NMCPHC HL7 formatted microbiology, chemistry, and pharmacy databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Inpatient Incidence Rates

Approximately 43.6% of the 2,238 incident CDI episodes from 2007-2013 were inpatient episodes. The overall inpatient CDI incidence rate peaked in 2012 and ended the surveillance period with a 5.6% decrease (Figure 11). The decrease in the overall inpatient incidence rate during the seven year surveillance period was influenced by the change in the distribution of the two most frequent types of acquistion among inpatient episodes, CA (30.0%) and HO (42.0%). Accordingly, among hospitalized beneficiaries, the frequency of CA acquistion increased from 24.8% in 2007 to 38.1% in 2013, while the frequency of HO acquisition decreased from 48.2% in 2007 to 30.5 % in 2013. Hence, CA inpatient incidence rates increased 35.7% while HO inpatient incidence rates decreased 38.5%. Additionally, HO incidence rates were 1-2 fold higher than CA incidence rates until 2012-2013, when CA rates surpassed HO rates.

Inpatient incidence rates attributed to hospital acquisition (combined HO and CO-HCFA) decreased 27.0% (data not shown). HO inpatient incidence rates were 1.4 to 3.1 fold higher than CO-HCFA rates, suggesting that HO cases have been the main driver of hospital acquistion rates. However, the relative difference between HO and CO-HCFA rates decreased in 2013.

Figure 11. Inpatient Incidence Rates per 10,000 Patient-Days by Acquisition among DON Beneficiaries, 2007-2013[a]

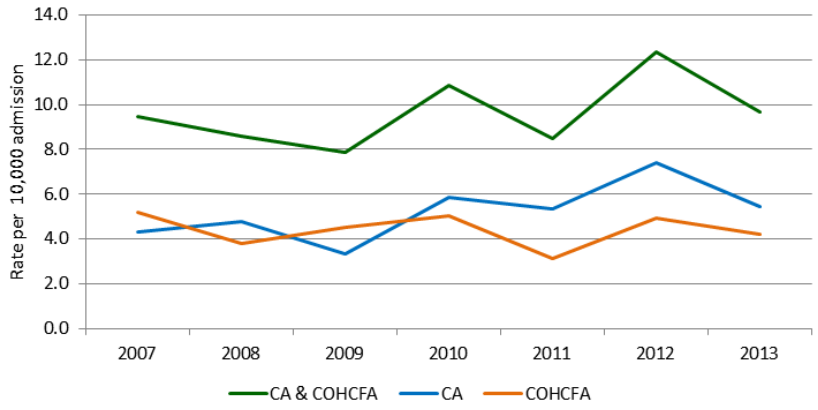


[a] *Clostridium difficile* Infection (CDI) inpatient incident episodes (N = 976).
Hospital-Onset (HO), Community Onset Healthcare Facility Associated (CO-HCFA) , Community Acquired (CA)
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and SIDR databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Admission Prevalence Rates

Overall admission prevalence (combined CA and CO-HCFA), a proxy estimate for CDI importation into MTFs, showed a peak year to year percentage change in 2010 of 38.0% with a second peak of 44.7% in 2012. However, there was an overall increase of just one percent across the surveillance period (Figure 12). Analysis of admission prevalence rates stratified by acquisition demonstrated annual CO-HCFA incidence rates were slightly higher than CA rates in 2007 and 2009, after which CA rates were consistently higher for the remainder of the period.

Figure 12. CDI Admission Prevalence Rates among DON Beneficiaries, 2007-2013[a]

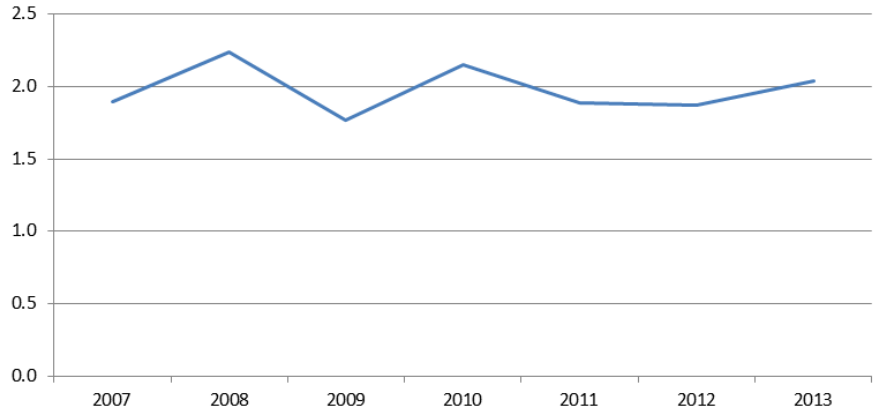


[a]*Clostridium difficile* Infection (CDI) admission prevalent episodes: (Community Associated (CA), n = 290) and (Community Onset Healthcare Facility Associated (CO-HCFA), n = 245).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and SIDR databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

CDI Outpatient Prevalence Rates

Outpatient prevalence rates at DON ambulatory clinics increased 5.3% from 2007-2013 with two year-to-year peaks in 2008 and 2010 (Figure 13).

Figure 13. Outpatient Prevalence Rates per 100,000 Patient-Encounters among DON Beneficiaries, 2007-2013[a]



[a]*Clostridium difficile Infection* (CDI) outpatient prevalent episodes (n = 1495).
Data Sources: NMCPHC HL7 formatted microbiology, HL7 formatted chemistry, and ambulatory databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, October 2014.

Discussion

This retrospective report summarizes trends for *C. difficile* infection for both DOD and DON beneficiaries from 2007-2013. CDI trends among both populations were similar and incidence rates among beneficiaries increased approximately 9.5% across the surveillance period. Most notably, the increase only occurred among beneficiaries with CA CDI. Several studies have shown CDI rate increases from 43% to 67% following the 2010 ASM recommendations to change to a more sensitive CD test.[34-35] In the DOD and DON, however, incidence rates estimated before and after the recommendations suggest that the switch from EIA to NAAT testing had only a minimal influence on overall CDI rates. Furthermore, the process of implementing a new test requires a considerable amount of time and effort. The clinical laboratory must perform an assessment regarding the needs of the local population, mandates of regulatory agencies, and the cost of the new testing. These decisions are not completed concurrently enterprise-wide thus; any effect of an increase in CDI incidence due to changes to a more sensitive and specific test may have been minimized by the number of laboratories making changes over time and the prevalence of CDI at each local MTF.

For most beneficiaries during the surveillance period, trends indicate that the vast majority of CDI is both acquired and identified in the community setting. This is a novel finding as existing CDI population-based surveillance and observational research studies have primarily targeted CDI incidence in hospitalized patients. More recently, CDI has been recognized for its occurrence in the community.[36-37] However, researchers have been slow to recognize CA CDI for two main reasons: first, CDI has historically been known as a nosocomial infection and therefore was likely underdiagnosed in non-hospitalized patients, and second, there was no

standardized surveillance definition until the Infectious Diseases Society of America (IDSA) proposed guidelines for their development in 2007.[2,25,30,38]

Although there was an increase in overall CDI incidence, there was no substantial change in the demographics of the beneficiary population that develops CDI. This study reports the burden of CDI is greater for individuals aged 45 years and older and nearly equal for males and females. The lack of gender-related difference in incidence rates is in contrast to studies performed in the general population that cite female gender as a CDI risk factor. However, studies that have observed gender differences have stated that there is currently no substantial evidence to support why these disparities occur.[8,9] The present study results are consistent with studies that report younger ages (median 50 years, range 1 month – 102 years) for patients with CA CDI compared to HO CDI (median 72 years, range 1 month – 99 years).[9,15,39,40]

Among the risk factors evaluated, the relatively low percentage of comorbidities among all beneficiaries with CDI suggests occurrence in a mostly healthy population. However, nearly 30% of beneficiaries had coexisting health problems, specifically diabetes, renal disease, COPD, and cancers, that put them at high risk for CDI and potentially poor health outcomes. In addition, approximately 30% of beneficiaries were not prescribed an antibiotic in the 90 days before the CDI episode, which contrasts with classical observations that indicate antibiotic exposure is a prerequisite for CDI occurrence.[2,41] Recent literature has recognized that a significant proportion of patients have not used antibiotics prior to the onset of CDI, especially among CA CDI.[10,16] This contradiction has caused researchers to question the current understanding of CDI as well as study biases, including ascertainment and detection biases, that could have contributed to studies finding 100% previous antibiotic exposure prevalence among CDI patients.[16] Nevertheless, antibiotics remain an important risk factor because of their ability to alter the normal flora in the colon, which allows CD to flourish and makes the bowel susceptible to infection.[1]

Among all inpatients, overall incidence rates showed a decrease for the surveillance period due mostly to a decrease in HO CDI. However, an unexpected interesting pattern emerged among hospitalized beneficiaries towards the latter part of the period from 2012-2013, when CA CDI incidence surpassed HO CDI incidence. As the emerging pattern has only been apparent for approximately two years, future reports will evaluate whether this is a continuing trend and provide plausible explanations for the change in acquisition. Even so, several studies have reported that CA CDI trends are increasing as is infection severity requiring colectomy among CDI patients.[42,43] In parallel, this retrospective report found HO incidence peaked in 2008 and then showed a decreasing trend through 2013. Reveles et al. reported similar trends among hospitalized patients citing the influence of infection prevention and antibiotic stewardship efforts for the decrease.[5] Additionally, the decreasing trend may be influenced by hospitals' shift to shorter lengths of stay, resulting in less risk for CDI for some inpatients.[44,45]

The decrease in HO CDI incidence also influenced the overall decrease in the CDI hospital acquisition rate, which includes both HO and CO-HCFA episodes. The decrease in HO cases is good news for infection prevention and antibiotic stewardship programs as their cumulative efforts may have influenced the decrease. However, when risk factors for transmission pressure

are considered, the relationship between admission prevalence (CDI importation into hospital by patients) and hospital acquisition (patients acquire CDI in hospital) must be evaluated as both types of acquisition contribute to patient reservoirs in the hospital. In the present report, the hospital acquisition incidence rate weighted by HO decreased, but the admission prevalence rate weighted by CA increased. Together, these facts illustrate that the reservoirs for CDI in the hospital are not decreasing; only that CDI importation is driving transmission pressure. Therefore, continued diligence is required to prevent transmission from person-to person and from indirect contact with the hospital environment that may lead to CDI development both during admission and after hospital discharge.

Antibiotic use, advanced age, and hospitalization continue to be important risk factors for CDI. However, among all beneficiaries, the majority of CDI episodes were acquired in the community setting in individuals aged 45 years and older. In addition, although most cases had an antibiotic prescribed in the 90 days before symptom onset, approximately 30% of beneficiaries did not have a history of antibiotic use. Therefore, providers should suspect CDI even among beneficiaries with no antibiotic use or healthcare facility exposures. Furthermore, the Society for Healthcare Epidemiology of America (SHEA) and IDSA clinical practice guidelines recommend that *C. difficile* be considered in the differential diagnosis for patients with moderate to severe diarrhea for three days or longer with fever or abdominal pain.[25] Additionally, the Association for Professionals in Infection Control and Epidemiology (APIC) recommends limiting the use of unnecessary antibiotics, favoring the use of antibiotics that are lower risk for CDI, and prescribing antibiotics for the shortest reasonable duration to decrease CDI incidence and recurrence.[46] The DOD and DON populations can benefit from these interventions to decrease both CDI incidence and antibiotic selective pressure that may influence the development of multidrug-resistant organisms.

Limitations

Acute diarrheal illness is a significant cause of morbidity and mortality worldwide. However, the specific etiologic agent often goes unrecognized as most diarrheal illness in the United States is among healthy individuals and is generally self-limiting. Thus, CDI incidence in the present report is likely underestimated when there is no microbiologic testing performed either when a patient's illness is not severe enough to present for medical care and in cases where the provider treats the diarrheal episode presumptively. In addition, recurrent CDI may be similarly underestimated. For example, if the provider initially determines that CD is the cause of the diarrheal episode and subsequently determines that the next episode is likely a continuation of the initial CDI episode further microbiologic testing may not be performed.

A prescription filled at a retail pharmacy rather than an MTF pharmacy would likely underestimate previous antibiotic use in the DOD beneficiary population. Efforts are underway in the EDC to enhance this analysis by including retail pharmacy data. In addition, because gastric acid suppressants are available over-the-counter, the present report could not measure use among beneficiaries who did not acquire these medications through prescription, thus gastric acid suppressant use is likely underestimated.

A comparison of comorbidity by each acquisition category (HO, CA, CO-HCFA, indeterminate) was not examined in the present report as the analysis was largely based on incidence, meaning that a beneficiary could potentially experience a new CDI incident episode every eight weeks. Consequently, the acquisition classification could vary with each new episode. For example, consider the following scenario: Beneficiary A has a diabetes comorbidity, a CA incident episode, and a subsequent HO incident episode. The demographic characteristics for this case, such as age and comorbidity, would be attributed to both acquisition types (CA and HO) and potentially lead to erroneous interpretations. This same logic was also applied to age group analysis, therefore age groups were not evaluated by acquisition category.

Databases used for this report do not contain data from purchased care providers, shipboard facilities, battalion aid stations, or in-theater facilities. Therefore, these results provide an estimate of CDI burden and clinical characteristics of CDI cases (i.e., previous antibiotic use and comorbidities) at fixed MTFs in the MHS.

A SIDR is created at discharge or transfer from an inpatient MTF for all TRICARE beneficiaries. For active duty personnel, this occurs for non-military medical treatment facility discharges as well. For all other beneficiaries, a SIDR is created upon discharge from an MTF. Patient encounter records depend on correct ICD-9-CM coding practices. Data for medical surveillance are considered provisional and medical case counts may change if the discharge record is edited after the patient is discharged from the medical treatment facility. As this is a retrospective report, it can be presumed with relative certainty that the records identified are the final and complete records for an inpatient encounter; however, the possibility does exist that records still may be modified, thereby altering the case counts and other clinical characteristics.

This report contains ambulatory data from health encounters at fixed MTFs in the MHS only. Records of ambulatory medical encounters depend on correct ICD-9-CM coding practices. Data for ambulatory medical surveillance are considered provisional and medical case counts may change between the time the data report is created and distributed. Additionally, because records are submitted into the system at different times, there may be patients who have had an outpatient encounter, but were not captured in the current data.

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Acronym/Abbreviation List

Acronym/Abbreviation	Definition
AD	Active duty
ASM	American Society for Microbiology
CA	Community-associated
CD	Clostridium difficile
CDC	Centers for Disease Control and Prevention
CDI	Clostridium difficile Infection
IBD	Inflammatory Bowel Disease
CHCS	Composite Health Care System
CLSI	Clinical and Laboratory Standards Institute
CA	Community-Acquired
CCI	Charlson Comorbidity Index
CO-HCFA	Community-Onset, Healthcare Facility Associated
COPD	Chronic Obstructive Pulmonary Disease
CY	Calendar Year
DMIS	Defense Medical Information System
DOD	Department of Defense
DON	Department of the Navy
EIA	Enzyme immunoassay
EDC	EpiData Center Department
FMT	Fecal Microbiota Transplantation
FDA	Food and Drug Administration
GI	Gastrointestinal
GDH	Glutamate Dehydrogenase
HL7	Health Level 7
H-2	Histamine-2
HO	Hospital-Onset
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IV	Intravenous
MEPRS	Medical Expense and Performance Reporting System
M2	MHS Data Mart
MDR	Multi-drug resistant
MHS	Military Health System
MTF	Military Treatment Facility
NAP1	North American Pulsed-Field Type 1
NMCPHC	Navy and Marine Corps Public Health Center
NAAT	Nucleic Acid Amplification Test
OCONUS	Outside of the continental United States
OP	Outpatient
PATCAT	Patient Category
PPIs	Proton Pump Inhibitors
PCR	Polymerase chain reaction
SHEA	Society for Healthcare Epidemiology of America
SIDR	Standard Inpatient Data Record
SSTI	Skin and soft tissue infection
UD	Unit dose
US	United States